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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/759,360	01/16/2001	Wolfgang Halfbrodt	SCH-1738	1922

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EXAMINER	
ROBINSON, BINTA M	
ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/759,360	HALFBRODT ET AL.	
	Examiner	Art Unit	
	Binta M. Robinson	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a) In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-42 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-42 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The 112, second paragraph rejection of claims 1,3, 4, 5, 6, 715, 16, 27-32 are withdrawn in light of applicant's amendment filed 10/6/03.

The group I restricted group, drawn to a compound of formula I in claim 1 where R1 and R2 equal optionally substituted phenyl, where the substituents on R1 and R2 do not come together to form a ring, R3 is as claimed and does not come together with another R3 to form a ring, R4, and R4', R5 and R5', are all moieties claimed except heterocyclic or heteroaryl rings, A are moieties claimed except a heterocyclic ring, B are all moieties claimed except tetrazolyl, X is as claimed, Y is as claimed, a method of treating a patient, a process of preparing a pharmaceutical composition, a pharmaceutical composition, has been examined. To clarify this restriction, compounds of group I will only be examined where none of the substituents on the R1, R2, R3 can come together to form methanediylbisoxy, ethane-1,2-diylbisoxy, propane-1,3-diyl, or butane-1,4-diyl.

(modified rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the

same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-42 in part are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for the radicals R1, R2, R5, independently and R5 and R5' coming together to form all possible 5-10 membered heteroaryl groups with 1-4 heteroatoms selected from N, S, and O, R4 and R4' coming together to form all C1-3 alkyl- 5-10 membered heteroaryl rings with 1-4 N, S, or O atoms or 5 to 10 membered heteroaryl rings with 1-4 N, S, or O atoms wherein two of said substituents for the aryl or heteroaryl group, if in the ortho position to one another, can be linked to one another in such a way that they jointly form methanedilybisoxy, ethane-1,2-diylbisoxy, propane-1,3-diyl, or butane-1,4-diyl. in claims 1-26 and where R1 equals monocyclic or bicyclic 5- to 10-membered heteroaryl group with 1-2 heteroatoms selected from the group that consists of N, S or O, whereby two of said substituents for the aryl or heteroaryl group, if in the ortho-position can be linked to one another in such a way that they jointly form methanediylbisoxy, ethane-1,2-diylbixoy, propane-1,3-diyl, butane-1,4-diyl. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims as recited are broader than the scope of enablement. The specification lacks direction or guidance for placing all of the alleged products in the possession of the public without inviting more than routine experimentation. The applicant is referred to ***In re Wands***, 858 F.2d 731, 737, 8

USPQ2d 1400, 1404 (Fed. Cir. 1988) which includes the incorporation of the 8 factors recited in ***Ex parte*** Foreman 230 USPQ 546 (Bd. Of App. And Inter 1986).

Claim(s) 15 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Microglia activation is a mechanism. The specific disease being treated by this inhibition is not stated. The specification must contain one practical utility in currently available form. Microglia activation must be related to a disease that needs to be improved and this disease needs to be recited. There is no reasonable assurance that these compounds will have all of the alleged properties or have the applicants supplied the supporting data. The applicant is referred to ***In re Fouche*** 169 USPQ 429 ccpa, 1971, MPEP 716.02 B. The applicant is referred to ***In re Wands*** (Fed. Cir. 1988) which includes the incorporation of the 8 factors recited in ***Ex parte Foreman*** 230 USPQ 546 (Bd. Of App. And Inter 1986).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1)the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art 6) the amount of direction provided by the inventor

7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).
In terms of factor 3 and 5, the state of the art and the level of predictability in the art cannot be predicted with any certainty beyond what specific test compounds /compositions and/or additional therapeutic agents should be used and are likely to provide productive results beyond those therapeutic compounds/compositions and/or additional therapeutic agents taught in the specification. Only example 307 was tested for its affect on microglial activation, 308 for its affect on cerebral ischemia, permanent middle cerebral artery occlusion, and 309 was tested for its affects on macrophage activation.

The nature of the invention

The nature of the invention is the synthesis of novel benzimidazole compounds and their use in the treatment and prophylaxis of diseases associated with microglial activation.

The state of the prior art

The state of the prior art is that a central step of the inflammation process is the activation of microglia. This is carried out diseases such as Alzheimer's disease. The microglia can remain for a prolonged period in the activated state, in which they produce and secrete various inflammation factors. These factors produce neuronal dysfunction and degeneration. Treatment of neuroinflammation to date

has been with steroidal anti-inflammatory agents (McGeer, P. L., Neurology 42, 447-449 (1992), (See Reference U) cytokine modulators, (McGeer, P. L., Brain Res. Rev 21:195-218) (See Reference V) and complement-cascade-inhibitors (Chen. Et. al. Neurobiol. Aging (1996) (See Reference W) These substances inhibit the syntheses or the action of individual inflammation factors. However, the claimed invention sets out to inhibit an earlier step in the inflammation process and thus prevent the development of any inflammatory factors.

The predictability or lack thereof in the art

The instant claimed invention is highly unpredictable as discussed below:

In the instant case, the claimed invention is highly unpredictable because of the absence of the claiming of the actual diseases that are said to be associated with microglial activation. The applicant has not shown that by inhibiting microglial activation, that specific diseases are being treated. The applicant has not claimed which diseases are actually being treated by inhibiting microglial activation. The nature of this art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance present

The direction present in the instant specification is that the compounds of claim 1 can inhibit microglial activation which helps in the treatment of diseases such as Alzheimer's which is said to be mediated by microglial activation. However, the specification is silent and fails to provide a correlation between the diseases listed in the specification and the inhibition of microglial activation. The specification fails to provide any experimental data of the effect of these compounds on microglial activation and specific diseases correlated with microglial activation.

The presence or absence of working examples

The applicant provides no working examples for the treatment of diseases association with microglial activation. Also, the compounds, which are disclosed in the specification, have no pharmacological data regarding the treatment of any disease. Also, the specification fails to provide working examples as to how the diseases associated with microglial activation in the specification can be treated by inhibition of microglial activation.

The breadth of the claims

The breadth of the claims is that the compound of claim 1 can treat any disease associated with microglial activation.

The quantify of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what specific diseases would be benefited by the inhibition of microglial activation and would furthermore then have to determine whether the claimed compounds would provide treatment of the disease by the

inhibition of microglial activation.

The level of skill in the art

The level of skill in the art is high. However, due to the unpredictability in the art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases

would benefit this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of claim 1 for the treatment of an NO-mediated disease. As a result, necessitating one of skill to perform an exhaustive search for which NO-mediated diseases can be treated by the compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which microglial

activation associated diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

As a result one of ordinary skill in the art could not predict what other types of therapeutic compounds/compositions and/or additional therapeutic agents, other than those taught in the specification; and with regards to the 7th and 8th wands factor, while the existence of working examples are limited to the aforementioned compounds/compositions as taught in the specification (example 307-309), an indeterminate quantity of experimentation would be necessary to determine all potential therapeutic compounds/compositions' effects on microglia activation.

In terms of the 8th Wands factors, undue experimentation would be required to make or use the invention based on the content of the disclosure due to the breadth of the claims, the level of predictability in the art of the invention, and the poor amount of direction provided by the inventor. Taking the above factors into consideration, it is not seen where the instant claim is enabled by the instant application.

(new rejections)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1, line 20, page 4 of the amendment filed 2/23/04, and all of the occurrences throughout claims 1-42, the phrase "C3-7 cycloalkyl-C0-3 alkyl" is indefinite because by definition, an alkyl group must have one carbon atom.

B. In claim 14, line 2, page 17, the phrase "one or more vehicles or diluents" is indefinite. A pharmaceutical composition must contain an inert, and pharmaceutically acceptable carrier.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim(s) 1-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuhnke et. al. (See Reference N). See the structures depicted below in the CAS reference 123:143893,

Kuhnke discloses the instant compounds, Acetic acid, [(1,2-dipheny;-1H-benzimidazol-6-yl)oxy]; Pentanoic acid, 5-[(1,2-diphenyl-1H-benzimidazol-6-yl)oxy]; Butanoic acid, 4-[(1,2-diphenyl-1H-benzimidazol-6-yl)oxy]; Pentanoic acid5-[[1-(nitrophenyl)-2-phenyl-H-benzimidazole-6-yl]oxy]-; hexanoic acid, 6-[[1-(4-nitrophenyl)-2-phenyl-1H-benzimidazol-6-yl]oxy-; pentanoic acid, 5-[[1-[4-(acetylamino)phenyl]-2-phenyl-1H-benzimidazol-6-yl]oxy]; pentanoic acid, 5-[[1-(3-nitrophenyl)-2-phenyl-1H-benzimidazol-6-yl)oxy]; hexanoic acid, 6-[[1-(3-nitropheny;)-2phenyl-1H-benzimdizol-6-yl]oxy]; pentanoic acid, 5-[[3-[[4-chlrorphenyl) sulfonyl]amino]phenyl]-2-phenyl-1H-benzimidazol-6-yl]oxy]; Pentanoic acid, 5-[[1-[4-[[4-chlorophenyl)sulfonyl]amino]phenyl]-2-phenyl-1H-benzimidazol-6-yl]oxy-; acetic acid, [(1,2-diphenyl-1H-benzimidazol-6-yl]-methyl ester; pentanoic acid, -5-[(1,2-diphenyl-1H-benzimidazol-6-yl)oxy]-methyl ester; butanoic acid, 4-{(1,2-diphenyl-1H-benzimidazol-6-yl)oxy]-ethyl ester; Pentanoic acid, 5-[[1-(4-nitrophenyl)-2-phenyl-1H-benzimidazol-6-yl]oxy-, methyl ester; Hexanoic acid, 6-[[1-(4-nitrophenyl)-2-phenyl-1H-benzimidazol-6-yl]oxy]-methyl ester; Pentanoic acid, 5-[[1-(4-aminophenyl)-2-pheynl-1H benzimidazole –6-yl oxy], methyl ester, monochloride; pentanoic acid, 5-[[1-(3-nitrophenyl)-2-phenyl-1H-benzimidazol-6-yl]oxy]-methyl ester; hexanoic acid, 6-[[1-(3-nitrophenyl)-2-phenyl-1H-benzimdazol-6-yl]oxy]-methyl ester; pentanoic acid, 5-[[1-(3-aminophenyl)-2-phenyl-1H-benzimdizole-6-yl]oxy-, methyl ester; pentanoic acid, 5-[[1-[3-[[4-chlorphenyl)sulfonyl]amino]phenyl]-2-phenyl-1H-benzimidazol-6-

yl]oxy]-, methyl ester;pentanoic acid, 5-[[1-[4-[[(4-chlorophenyl)sulfonyl]amino]phenyl]-2-phenyl-1H-benzimidazol-6-yl]oxy]-, methyl ester. At pages, 7-9, see the instant compounds.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuhnke et. al. (See Reference N).

Kuhnke et. al. teaches the instant compound as shown in Formula I, where R1 and R2 can independently be Ph optionally mono or disubstituted with halogen, alkoxy, carboxyl, R3 and R4 are optionally H, halogen, 1-6C alkyl, 1-6C alkoxy, 1-6 alkoxycarbonyl, COHNR6, NO2, NH2 an A is a direct bond, R6 is H, or 1-6 C alkyl and R5 is COOH. At page 9, see formula I. The difference between the prior art compound and the instantly claimed compounds is the teaching of a generic compound versus a disclosed species. The exemplified species anticipates the instant compounds in the application. There is enough guidance in the art to make and use all of the generically disclosed compounds. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds. For instance,

at pages 7- 8, see the compound, pentanoic acid, 5-[[1-(3-nitrophenyl)-2-phenyl-1H-benzimidazol-6-yl]oxy]-methyl ester, where a disclosed species is exemplified. It would be expected that all generic teachings would operable in a similar manner to the compounds in the instant claims. Accordingly, the compounds are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta Robinson whose telephone number is (703)306-5437. The examiner can normally be reached on Monday through Friday from 9:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. John Kight, can be reached on (703)308-0204. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

BMR
March 19, 2004

CEILA CHANG
PRIMARY EXAMINER
GROUP ~~1200~~ 1625